REMARKS

Claims 76-82 are currently pending in this application. Claims 78, 81, and 82 are withdrawn from consideration. Claim 77 is rejected under 35 U.S.C. § 112, first paragraph, for lack of written description, while claims 76, 77, 79, and 80 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 76, 77, 79, and 80 are rejected under 35 U.S.C. § 102(b) for anticipation by Satoh et al. (U.S. Patent No. 5,560,908; hereinafter "Satoh") in view of Hsu et al. (Cell 84:299-308, 1996; hereinafter "Hsu"), and under 35 U.S.C. § 102(e) for anticipation by Faustman (U.S. Patent No. 6,660,487; hereinafter "Faustman"). Finally, claims 76, 77, 79, and 80 are rejected for obviousness-type double patenting over claim 9 of U.S. Patent No. 6,660,487 and provisionally rejected for obviousness-type double patenting over claims 16-30, 65-73, and 91-108 of copending U.S. Serial. No. 10/851,983. By this reply, Applicants address each of the rejections.

Declaration under 37 C.F.R. § 1.67(a)

The Examiner states that the declaration filed with the application on February 10, 2004, is defective because it contains non-initialed and/or non-dated alterations. In response, Applicants submit a supplemental application data sheet that corrects Inventor Hayashi's residence address. Applicants believe the requirements of 37 C.F.R. § 1.52(c) have been met.

Formalities

The Examiner states that present claims 76, 79, and 80 are entitled to claim benefit to the filing date of U.S. Serial No. 09/031,629, now U.S. Patent No. 6,617,171, which was filed on February 27, 1998, but that claim 77 is only entitled to claim benefit to the filing date of the present application, which is February 10, 2004, unless evidence to the contrary is submitted (Office Action, p. 2). Applicants direct the Examiner to col. 5, lines 18-42, col. 11, line 51, through col. 12, line 11, of U.S. Patent No. 6,617,171, which teaches:

> Examples of autoimmune diseases include, but are not limited to, diabetes...Another aspect of the present invention is a method of treating an autoimmune disease in a mammal, comprising administering to a mammal suspected of suffering from an autoimmune disease an agent which restores NFκB activity in an amount and for a time sufficient to result in normal NFκB activity in

> the mammal...It is preferred that the protein is selected from the group that includes...*tumor necrosis factor-α*... In another preferred embodiment, the autoimmune disease is selected from the group that includes those diseases listed above. (Emphasis added.)

Thus, the '171 patent provides clear support for the subject matter of present claim 77. For this reason, claim 77 is entitled to claim the benefit of priority to the filing date of the '171 patent, which is February 27, 1998. Applicants respectfully request acknowledgement from the Office on this point.

In addition, the Examiner requests that Applicants amend the first line of the specification to update the status of the priority documents. The specification has been amended to reflect the current status of the two priority documents.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claim 77 is rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that the specification does not provide sufficient written support for the treatment of "generic" autoimmune disease or "generic" diabetes by administering TNF-α. Applicants respectfully traverse this rejection.

As is discussed above, the subject matter of present claim 77 is fully described in the priority application, U.S. Serial No. 09/031,629, now U.S. Patent No. 6,617,171, and is found in the present application at, e.g., page 21, lines 5-8 and 15-22, and page 22, lines 8-9, as is acknowledged by the Examiner in the present Office Action (see Office Action, p. 6). Thus, the present application provides clear support for the treatment of generic autoimmune diseases, including diabetes, by administering TNF-α to a patient having an autoimmune disease. Applicants respectfully submit that the rejection of claim 77 for lack of written description can now be withdrawn.

Enablement

Claims 76, 77, 79, and 80 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states:

> the instant specification does not provide sufficient direction or guidance for one of ordinary skill in the art to treat any autoimmune disease in a mammal by administering TNF-α. Indeed, the art prior to applicant's earliest claimed priority date demonstrated that TNF-α **inhibitors** are useful in treating human disease and that the level of TNF-α expression is correlated with autoimmune disease severity. (Office Action, p. 6.)

Applicants respectfully traverse this rejection.

The M.P.E.P. § 2164.01(b) states that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." Applicants have plainly met this standard.

Independent claim 76 is directed to a method for treating a mammal having an autoimmune disease by administering a therapeutically effective amount of a substance that stimulates a signaling pathway that activates NFκB. Dependent claims 77 and 79 are directed to substances that stimulate a signaling pathway that activates NFκB (i.e., TNF-inducing substances), such as TNF-α, while dependent claim 80 recites the types of autoimmune diseases in mammals that can be treated by the method of present independent claim 76. The invention recited in present claims 76, 77, 79, and 80 is based on Applicants' discovery that autoreactive immune cells present in mammals having autoimmune disease exhibit defects in their NF-κB signaling pathways, which result in an increased sensitivity to TNF-induced cell death. This discovery is clearly disclosed in the present specification at, e.g., page 113, line 16, through page 116, line 2, page 124, lines 20-22; and page 126, line 5, through page 127, line 6). In particular, Figs. 8A-8D provide clear evidence that the NF-κB signaling pathway is defective in autoreactive immune cells from NOD mice, which is an accepted animal model for treatment of type 1 (autoimmune) diabetes mellitus, Sjogren's syndrome, and lupus in humans, while Figures 13A-13D provide evidence that exposure of autoreactive immune cells from NOD mice to TNF-α results in autoreactive immune cell death, as determined by cell viability and DNA fragmentation assays.

Based on this discovery, Applicants recognized that defects in NF-κB signaling was a

common denominator across several autoimmune diseases, including, e.g., Type I diabetes, lupus, Crohn's disease, Sjogren's syndrome, autoimmune regulator diseases [autoimmune polyendocrinopathy syndrome (APS)-1 or autoimmune polyendorinopathy candidasis ectodermal dystrophy], hypothyroidism, multiple sclerosis, psoriasis, and scleroderma, and that administration of TNF-inducing substances to mammals having an autoimmune disease would treat the disease by eliminating autoreactive immune cells responsible for, or responsible for exacerbating, the disease condition.

As evidence of the efficacy of the invention, Applicants direct the Examiner to the enclosed Declaration of the co-inventor, Dr. Denise Faustman, who attests that NF-κB dysregulation has been found not only in humans but in at least two animal models of autoimmune disease (see ¶ 4 of the Declaration). Dr. Faustman states that her data confirm that even disparate autoimmune diseases result from defects in NF-κB signaling pathways. Moreover, as is discussed in the Declaration, Dr. Faustman's data confirm that multiple, disparate autoimmune diseases can be treated by administering a TNF-α agonist, such as TNF-α or other TNF-α inducing substance, to a mammal, which promotes cell death in the autoreactive immune cells.

At ¶ 6 of the Declaration, Dr. Faustman states that she validated the methods of the invention by showing that autoreactive immune cells obtained from human patients having several disparate autoimmune diseases, including, e.g, Type I diabetes, lupus, scleroderma, Sjogren's syndrome, hypothyroidism, multiple sclerosis, Crohn's disease, and psoriasis, undergo cell death when exposed to TNF-α agonists, such as TNF-α (see Exhibit A). Her observations confirm that defects in the NF-κB signaling pathways are not unique to autoreactive T cells from NOD mice, or even from human patients having type I diabetes, but rather that these defects are present in autoreactive T cells from human patients having several different types of autoimmune diseases.

Dr. Faustman also states that she has observed TNF-agonist-induced autoreactive T cell death in samples from over 1000 type 1 diabetics studied, and in her studies of greater than 50 patients with lupus, greater than 8 patients with scleroderma, greater than 8 patients with Sjogren's syndrome, greater than 50 patients with hypothyroidism, greater than 20 patients with

multiple sclerosis, greater 15 patients with Crohn's disease, and 6 patients with psoriasis (see ¶ 6 of the Declaration). Furthermore, Dr. Faustman attests that her results confirm that autoreactive immune cells can be distinguished from normal cells by not only defects in NFkB signaling on a molecular level, but also on a cellular level by targeted cell death via TNF agonism, a symptom of the NFkB interruption (see ¶ 6 of the Declaration).

In ¶¶ 7 and 8 of the Declaration, Dr. Faustman confirms that, in addition to TNF-α, other TNF-α agonists promote autoreactive immune cell death. In particular, Dr. Faustman states that she has observed that TNF agonist antibodies promote cell death in autoreactive immune cells from patients having diabetes, lupus, multiple sclerosis, psoriasis, Crohn's and rheumatoid arthritis (see Exhibit B), while other substances, such as BCG, which induce endogenous TNF-α expression, promote autoreactive immune cell death when administered to autoreactive animals with type I diabetes, lupus, or Sjogren's syndrome and successfully delay onset of disease in these animals. Dr. Faustman also states that even a single administration of a TNF inducer to an autoimmune mouse delays for several months the appearance of autoimmune disease in normal mice that receive transfers of cells from an autoimmune mouse (see ¶ 8 of the Declaration and Exhibit C).

The data presented in the Declaration of Dr. Faustman clearly confirms that TNF-inducer substances, such as TNF-α, TNF agonist antibodies, and BCG, can be used to selectively eliminate autoreactive immune cells in mammals having autoimmune diseases, which thereby treats autoimmune disease in these mammals. Thus, the Declaration of Dr. Faustman supports Applicants' position that the methods recited in present claims 76, 77, 79, and 80 are fully enabled.

Finally, Applicants wish to address the Examiner's statement that

> the teachings of the instant specification do not enable the skilled artisan to use TNF-α to treat any autoimmune disease, and based upon the teaching in the art undue experimentation would be required of the skilled artisan to treat autoimmune disease with TNF-α because for many diseases the art teaches this would only serve to exacerbate symptoms. (Office Action, p. 6.)

In response, Applicants direct the Examiner to ¶ 9 of the Declaration of Dr. Faustman, which addresses the apparent paradox between the prior art and the invention recited in present

claims 76, 77, 79, and 80. Dr. Faustman states that current therapies on the market for treatment of rheumatoid arthritis and Crohn's disease, such as REMICADE® (infliximab), ENBREL® (etanercept), and HUMIRA® (adalimumab), which remove or inactivate serum TNF, can certainly remove inflammation, and thus improve the symptoms of autoimmunity, yet her data and other pre- and post-filing date publications suggest that anti-TNF therapy could actually exacerbate or elicit new autoimmune disease in some patients. Dr. Faustman points out that neutralization of TNF by drug therapy with anti-TNF has been shown to induce, in some cases, new or exacerbated autoimmunity (see ¶ 9 of the Declaration and Exhibit D).

Thus, in summary, Dr. Faustman's data supports and further validates her claim that the methods of present claims 76, 77, 79, and 80 can be performed successfully to treat a mammal diagnosed with autoimmune disease by administering a substance that stimulates a signaling pathway that activates NFκB, e.g., TNF agonists, such as TNF-α. Accordingly, the enablement of claims 76, 77, 79, and 80 has been demonstrated. For this reason, Applicants respectfully request that the rejection of claims 76, 77, 79, and 80 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 76, 77, 79, and 80 stand rejected under 35 U.S.C. § 102(b) for anticipation by Satoh in view of Hsu. The Examiner states that "Satoh teaches a method of treating a mammal, in particular a human, having an autoimmune disease, in particular diabetes, comprising administering a therapeutically effective amount of TNF-α" (Office Action, p. 7). Applicants respectfully traverse this rejection.

Present claims 76, 77, 79, and 80 are directed to a method for treating a mammal having an autoimmune disease by administering a therapeutically effective amount of a substance that stimulates a signaling pathway that activates NFκB, e.g., TNF-α. Satoh only discloses administering TNF-α to patients having non-insulin dependent diabetes mellitus (NIDDM), which is not an autoimmune disease (see, e.g., Sherwin, Cecil Textbook of Medicine, 21st Edition, Chapter 242, page 1263, edited by Goldman and Bennett, WB Sauders Company; a copy

of which is enclosed). Hsu does not overcome this deficiency because it fails to teach or suggest the treatment of a mammal having an autoimmune disease by administering to the mammal a substance, such as a TNF-inducing substance, that activate NFκB, as is recited in present claims 76, 77, 79, and 80. Because neither Satoh nor Hsu, either alone or in combination, teaches all of the elements of present claims 76, 77, 79, and 80, Applicants respectfully request that the rejection of present claims 76, 77, 79, and 80 under 35 U.S.C. § 102(b) for anticipation by Satoh in view of Hsu be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 76, 77, 79, and 80 also stand rejected under 35 U.S.C. § 102(e) for anticipation by Faustman. Applicants respectfully traverse this rejection.

As is discussed above, the present application, including the subject matter of pending claims 76, 77, 79, and 80, is entitled to claim benefit to the filing date of U.S. Serial No. 09/031,629, which is February 27, 1998. The earliest priority date for Faustman is March 10, 1999. For Faustman to constitute prior art to the present application it must have a filing date earlier than the effective filing date of the present application, which it does not. MPEP § 706.02(a); 35 U.S.C. § 102(e). Thus, the disclosure of Faustman is not prior art to the present application, and Applicants respectfully request that this rejection be withdrawn.

Obviousness-Type Double-Patenting Rejection

Claims 76, 77, 79, and 80 are rejected for obviousness-type double patenting over claim 9 of U.S. Patent No. 6,660,487, and provisionally rejected for obviousness-type double patenting over claims 16-30, 65-73, and 91-108 of copending U.S. Serial. No. 10/851,983. When the pending claims are found to be otherwise allowable except for these grounds of rejection, Applicants will address the rejections, including consideration of whether to file a terminal disclaimer.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including June 15, 2007, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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